

**N-PHENYL-3-CYCLOPROPYLPYRAZOLE-4-CARBONITRILES AS  
ECTOPARASITICIDAL AGENTS**

**FIELD OF THE INVENTION**

1 The present invention is directed to novel compounds and compositions  
5 useful in preventing and treating ectoparasiticidal infestation, and more particularly,  
to new carbonitrile compounds and formulations which are highly efficacious in  
controlling external parasites in both companion animals and livestock.

**BACKGROUND OF THE INVENTION**

10 Virtually all commercial and most companion animals are affected by  
ectoparasites. The outcome associated with ectoparasitism in said animals is  
generally clinical disease and subclinical conditions that decrease performance.  
Arthropods, such as Phthiraptera (lice) and Diptera (flies), are among the most  
economically important ectoparasites in animal production. Arthropods, such as  
15 Siphonáptera (fleas) and Acarina (ticks) are highly pesteriferous to companion  
animals and humans and are significant carriers of disease. Ectoparasitic infection  
and infestation not only seriously effect the economies of raising meat-producing  
animals but are also a source of great concern for companion animals and humans.  
New, economic alternative methods and compositions for the prevention, treatment  
and control of ectoparasites in warm-blooded animals are constantly being sought.

20 Important agronomic and companion animals such as cattle, sheep, horses,  
goats, pigs, camels, water buffalo, donkeys, rabbits, fallow deer, reindeer, minks,  
chinchillas, raccoons, chickens, geese, turkeys, ducks, dogs, cats or the like are  
prone to attack and infestation by biting and sucking ectoparasitic insects such as  
Diptera, Muscidae, Acarina or Siphonáptera. In particular, Diptera: Muscidae such  
25 as *Musca autumnalis* (face flies), *Haematobia irritans* (horn flies) *Stomoxys calcitrans*  
(stable flies), heel flies, tsetse flies, blow flies or the like are breeders of filth and  
vectors of disease and are serious pests of animals such as cattle, horses and  
sheep, and, Diptera: Hippoboscidae (louse flies) such as *Melophagus ovinus* (sheep  
ked), which is a serious parasite of sheep are problematic in animal production.

30 Acarina, including ticks, e.g., *Ixodes* spp., *Boophilus microplus*, *Amblyomma*  
spp., *Hyalomma* spp., *Rhipicephalus* spp., e.g., *Rhipicephalus sanguineus*,  
*Rhipicephalus appendiculatus*, *Haemaphysalis* spp., *Dermacentor* spp., e.g.

*Dermacentor variabilis* or the like are serious pests and vectors of disease for man and domestic or companion animals.

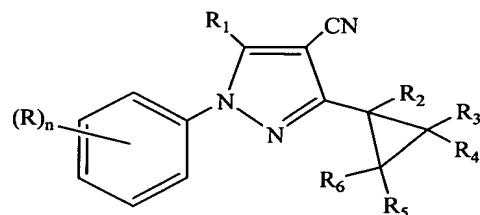
Among the Phthiraptera families known to be parasites of animals are: Trichodectidae such as *Bovicola bovis* (important cattle-biting louse), *B. ovis* (sheep-biting louse) or *B. equi* (horsebiting louse); Haematopinidae such as *Haematopinus suis* (hog louse), or *H. asini* (horse sucking louse); Linognathidae such as *Linognathus stenopsis* (goat sucking louse) or *L. vituli* (long-nosed cattle louse); or the like.

Among the Siphonaptera families known to infest companion animals is 10 *Pulicidae* such as *Archaeopsyllinae* (cat and dog fleas), *Spilopsyllinae* (rabbit fleas), or the like.

The animal health care industry has developed a formidable arsenal of compositions to treat and prevent ectoparasitic infection. Unfortunately, many compounds have lost considerable efficacy over time due to the development of 15 resistant strains of parasites, as well as other factors. What is therefore needed in the art are new compounds and formulations which can be utilized in the ongoing battle to maintain livestock and companion animals free of disease-bearing pests.

#### SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



20

(I)

or a pharmaceutically acceptable salt thereof wherein

R is halogen, OR<sub>7</sub>, SO<sub>m</sub>R<sub>8</sub>, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>6</sub>haloalkyl or an optionally substituted C<sub>1</sub>-C<sub>6</sub>alkyl group;

n is 0 or an integer of 1, 2 or 3;

25 m is 0 or an integer of 1 or 2;

R<sub>1</sub> is H, halogen, NO<sub>2</sub>, NR<sub>9</sub>R<sub>10</sub>, NR<sub>11</sub>COR<sub>12</sub>, NCHNR<sub>9</sub>R<sub>10</sub> or NCHOR<sub>13</sub>;

$R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are each independently H, halogen or a  $C_1$ - $C_4$ alkyl, aryl or heteroaryl group each optionally substituted;

$R_7$  is H or a  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, aryl or heteroaryl group each optionally substituted;

5       $R_8$  is a  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, aryl or heteroaryl group each optionally substituted;

$R_9$  and  $R_{10}$  are each independently H,  $C_1$ - $C_4$ haloalkyl or a  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, aryl or heteroaryl group each optionally substituted or  $R_9$  and  $R_{10}$  may be taken together with the atom to

10     which they are attached to form a 5- to 7-membered ring optionally containing 1 or 2 additional heteroatoms selected from O, N or S;

$R_{11}$  is H,  $COR_{12}$  or an optionally substituted  $C_1$ - $C_4$ alkyl group;

$R_{12}$  is a  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, aryl or heteroaryl group each optionally substituted (including  $C_3$  –  $C_7$  cycloalkyl); and

15      $R_{13}$  is H or a  $C_1$ - $C_6$ alkyl, aryl or heteroaryl group each optionally substituted;

and

the stereoisomers and tautomers thereof.

The present invention also provides a compound of formula I as set forth above, but with the further proviso that  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are not all –H, unless  $R_1$  is

20     halogen.

The present invention also provides a method for the prevention, amelioration or control of ectoparasitic infection or infestation in a homeothermic animal which comprises providing to a homeothermic animal in need thereof a prophylactically, therapeutically or pharmaceutically effective amount of a compound of formula I.

25     This invention also provides a composition which comprises a pharmaceutically acceptable carrier and an ectoparasitically effective amount of a compound of formula I.

The invention further provides a composition and method for treating ectoparasitic infection which utilizes the compound of formula I above, with the

30     further proviso that  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are not all –H, unless  $R_1$  is halogen.

It is an object of the present invention to provide compounds which are useful for veterinary medicine and livestock husbandry and in the maintenance of public health against arthropods which are ectoparasites upon homeothermic animals.

It is another object of this invention to provide an effective method for the prevention, treatment or control of ectoparasitic infection or infestation in homeothermic animals.

It is also an object of this invention to provide an ectoparasiticidal composition 5 suitable for use on animals and humans.

Further objects and features of the invention will become apparent from the detailed description set forth herein.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an N-phenyl-3-cyclopropylpyrazole-4-10 carbonitrile of formula I, above. Unless otherwise specified, "compounds of formula I" includes all the embodiments thereof hereinafter described. Surprisingly, it has now been found that compounds of formula I may be useful in the fields of veterinary medicine and livestock husbandry and in the maintenance of public health against ectoparasites and their infection or infestation.

As used in this specification and the appended claims, the term halogen 15 designates F, Cl, Br or I, and the term heteroaryl designates a C<sub>5</sub>-C<sub>10</sub> aromatic ring system containing 1, 2 or 3 heteroatoms, which may be the same or different, selected from N, O or S. Such heteroaryl ring systems include pyrrolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furyl, thienyl, quinolinyl, isoquinolinyl, indolyl, 20 benzothienyl, benzofuranyl, benzisoxazolyl and the like. The term aryl designates a carbocyclic aromatic ring system such as phenyl, naphthyl, anthracenyl or the like. The term haloalkyl as used herein designates a C<sub>n</sub>H<sub>2n+1</sub> group having from one to 2n+1 halogen atoms which may be the same or different and the term haloalkoxy as used herein designates an OC<sub>n</sub>H<sub>2n+1</sub> group having from one to 2n+1 halogen atoms 25 which may be the same or different.

In the specification and claims, when the terms C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, aryl or heteroaryl are designated as being optionally substituted, the substituent groups which are optionally present may be one or more of those customarily employed in the development of veterinary or pharmaceutical 30 compounds or the modification of such compounds to influence their structure/activity, persistence, absorption, stability or other beneficial property. Specific examples of such substituents include halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, alkanediyl, haloalkyl, alkoxy, haloalkoxy, amino,

alkylamino, dialkylamino, formyl, alkoxy carbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocyclyl or cycloalkyl groups, preferably halogen atoms or lower haloalkyl or lower haloalkoxy groups. Typically, 0-3 substituents may be present, 5 preferably 1 or 2. When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, more preferably up to 4 carbon atoms. Optionally substituted C<sub>1</sub> – C<sub>6</sub> alkyl includes methyl substituted by C<sub>2</sub> – C<sub>6</sub> alkanediyl, i.e. includes C<sub>3</sub> – C<sub>7</sub> cycloalkyl.

10                   Compounds of the invention may exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers, atropisomers and geometric isomers. One skilled in the art will appreciate that one stereoisomer may be more active or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the 15 skilled artisan knows how to separate, enrich or selectively prepare said stereoisomers. Accordingly, the present invention comprises compounds of Formula I, the stereoisomers thereof and the tautomers thereof. The compounds of the invention may be present as a mixture of stereoisomers, individual stereoisomers, or as an optically active or enantiomerically pure form.

20                   Compounds of formula I may exist in one or more tautomeric forms that may give rise to geometric isomers around the tautomeric double bond. One skilled in the art will recognize that said tautomers often exist in equilibrium with one another. As these tautomers interconvert under environmental and physiological conditions, they provide the same useful biological effects. The present invention 25 includes mixtures of such tautomers as well as the individual tautomers of compounds of formula I.

Preferred compounds of the invention include compounds of formula I wherein R is halogen or haloalkyl. Another group of preferred compounds are those formula I compounds wherein R<sub>1</sub> is H, halogen or NR<sub>9</sub>R<sub>10</sub>. A further group of 30 preferred compounds are those of formula I wherein R<sub>5</sub> and R<sub>6</sub> are H.

More preferred compounds of the invention include formula I compounds wherein R is halogen or haloalkyl; n is 3; and R<sub>2</sub> is H, halogen, methyl or optionally

substituted phenyl. Another group of more preferred compounds are those of formula I wherein R is Cl or CF<sub>3</sub>; n is 3; R<sub>2</sub> is Cl or CH<sub>3</sub>; and R<sub>1</sub> is H or Cl.

Especially preferred compounds include those having the formula I set forth above, but with the further proviso that R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are not all -H, unless R<sub>1</sub> is 5 halogen.

Exemplary of some of the preferred compounds of the invention are

5-chloro-3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

3-(2,2-dichloro-1-methylcyclopropyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonitrile;

3-(2,2-dichloro-1,3-dimethylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

3-(2,2-dibromo-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

3-(2,2-dibromo-1-methylcyclopropyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonitrile;

3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

5-chloro-3-(2,2-dibromo-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

5-amino-3-(2,2-dibromo-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

5-bromo-3-(2,2-dibromo-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

5-amino-3-(2,2-dichloro-1-methylcyclopropyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonitrile;

5-chloro-3-cyclopropyl-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

5-chloro-3-(2,2-dichloro-1-methylcyclopropyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonitrile;

5-bromo-3-(2,2-dichloro-1-methylcyclopropyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonitrile;

5-bromo-3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

5 3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-nitro-1H-pyrazole-4-carbonitrile;

3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-iodo-1H-pyrazole-4-carbonitrile;

3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-10 (dimethylamino)-1H-pyrazole-4-carbonitrile;

3-(2,2-dichloro-1-methylcyclopyrazol)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-(diethylamino)-1H-pyrazole-4-carbonitrile;

5-[cyclopropanecarbonyl]amino]-3-(2,2-dichloro-1methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile;

15 N-{4-cyano-5-(2,2-dichloro-1-methyl-cyclopropyl)-2-[2,6-dichloro-4-(trifluoromethyl)-phenyl]-2H-pyrazol-3-yl}-formimidic acid methyl ester;

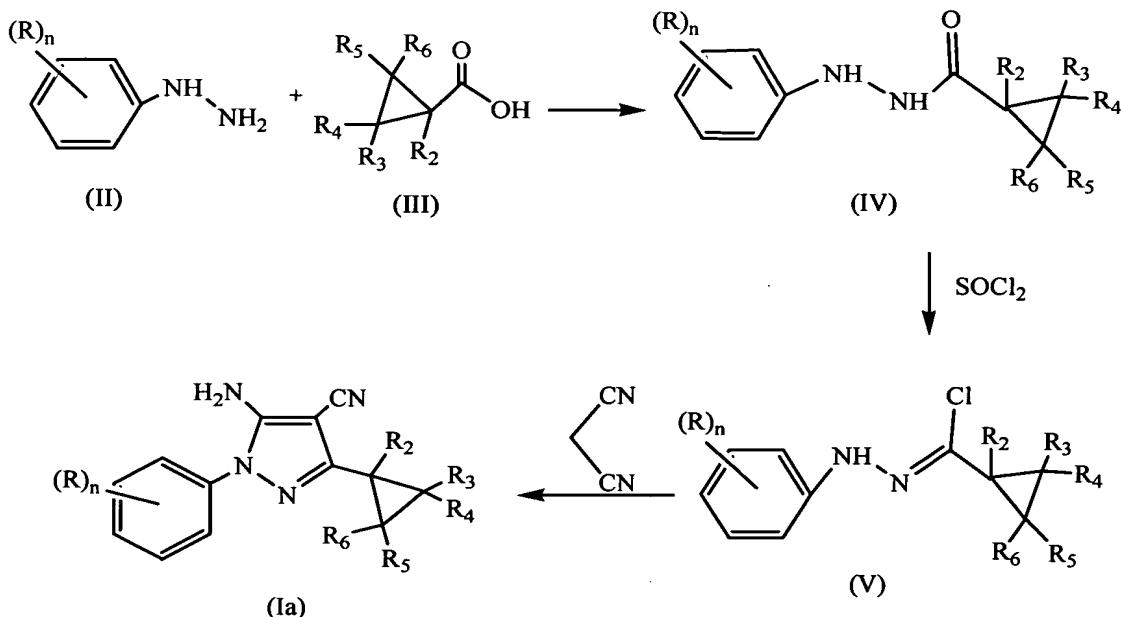
N-{4-cyano-5-(2,2-dichloro-1-methyl-cyclopropyl)-2-[2,6-dichloro-4-(trifluoromethyl)-phenyl]-2H-pyrazol-3-yl}-formimidic acid propyl ester;

N-{4-cyano-5-(2,2-dichloro-1-methyl-cyclopropyl)-2-[2,6-dichloro-4-(trifluoromethyl)-phenyl]-2H-pyrazol-3-yl}-formimidic acid ethyl ester;

20 the stereoisomers thereof or the tautomers thereof.

Compounds of formula I may be prepared using conventional synthetic techniques and, if required, standard separation and isolation techniques. In one preferred embodiment of the method of this invention, compounds of formula I wherein R<sub>1</sub> is NH<sub>2</sub> (Ia) may be prepared by reacting a phenyl hydrazine of formula II with a cyclopropylcarboxylic acid of formula III to give the intermediate of formula IV; reacting the formula IV intermediate with a chlorinating agent such as thionyl chloride to give the chloroenamine of formula V; and reacting the formula V enamine with malononitrile to give the desired product of formula Ia. This method is shown in flow diagram I.

## FLOW DIAGRAM I



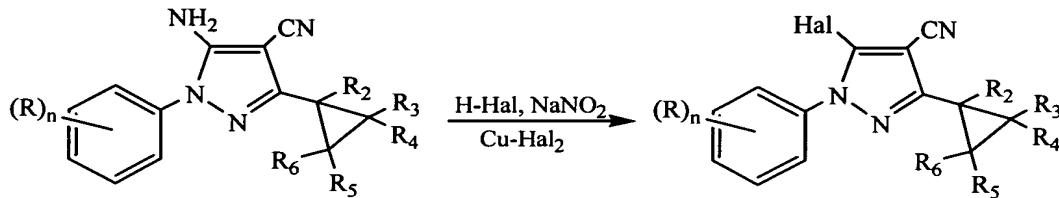
The compounds of formula Ia may be used as chemical intermediates to 5 prepare the other compounds having formula I using standard derivatization procedures. For instance, the compounds having formula Ia may be used to prepare the other compounds having formula I in which  $\text{R}_1$  is  $\text{NR}_9\text{R}_{10}$  by standard methods of converting primary amines into secondary amines and tertiary amines, for example, by standard alkylation procedures. In the compounds having formula I in which  $\text{R}_1$  is 10  $\text{NR}_9\text{R}_{10}$ ,  $\text{R}_9$  and  $\text{R}_{10}$  are preferably independently selected from H and  $\text{C}_1\text{-C}_6$ alkyl. The compounds of formula I in which  $\text{R}_1$  is  $\text{NR}_9\text{R}_{10}$  (including the compounds having formula Ia) may be recovered in the form of their free bases or in the form of their pharmaceutically acceptable acid addition salts. The compounds of formula Ia and those having formula I in which  $\text{R}_1$  is  $\text{NHR}_{10}$ ,  $\text{R}_{10}$  being an optionally substituted  $\text{C}_1\text{-C}_4$ alkyl group, may be used to prepare the compounds having formula I in which  $\text{R}_1$  is 15  $\text{NR}_{11}\text{COR}_{12}$  by standard methods of converting primary amines into amides and imides and secondary amines into amides. Such methods may use reactive derivatives of the carboxylic acid  $\text{R}_{12}\text{CO}_2\text{H}$  where  $\text{R}_{12}$  is as defined above.  $\text{R}_{12}$  is preferably  $\text{C}_1\text{-C}_6$  alkyl or  $\text{C}_3\text{-C}_7$  cycloalkyl. Similarly to the aforesaid derivitization,

using formula Ia as substrate and employing the procedures described in US 5,814,652 or Journal of Heterocyclic Chemistry, 2000, 37, 1617, compounds of formula I wherein R<sub>1</sub> is NCHOR<sub>13</sub> or NCHNR<sub>9</sub>R<sub>10</sub>, respectively, may be prepared.

The compounds of formula Ia may be used as chemical intermediates to 5 prepare the compounds having formula I in which R<sub>1</sub> is halogen or nitro via diazonium salts as intermediates. For instance, the compounds having formula I in which R<sub>1</sub> is nitro may be prepared in known manner by treatment of diazonium salts with sodium nitrite in the presence of cuprous ions in neutral or alkaline solution. The compounds having formula I in which R<sub>1</sub> is fluorine may be prepared via diazonium 10 salts by the Balz-Schiemann reaction. The other compounds of formula I wherein R<sub>1</sub> is halogen (Ib) may be prepared by reacting the formula Ia compound with, in the case wherein the halogen is Cl, concentrated HCl, NaNO<sub>2</sub> and CuCl<sub>2</sub>. This reaction is shown in flow diagram II wherein Hal represents Cl, Br or I.

#### FLOW DIAGRAM II

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Compounds of formula I wherein R<sub>1</sub> is H may be prepared using conventional deamination techniques such as reacting a compound of formula Ia with amylnitrite or n-pentylnitrite, as described in EP 303118.

Advantageously, it has now been found that an N-phenyl-3-cyclopropylpyrazole-4-carbonitrile compound of formula I may be used to effectively 20 control, prevent or ameliorate infection and infestation of ectoparasites on homeothermic animals, such as cattle, sheep, horses, goats, pigs, camels, water buffalo, donkeys, rabbits, fallow deer, reindeer, minks, chinchillas, raccoons, chickens, geese, turkeys, ducks, dogs, cats and the like.

Ectoparasites against which a compound of Formula I is useful include biting 25 and sucking ectoparasitic insects such as Diptera, Muscidae, Acarina or Siphonaptera, in particular, Diptera: Muscidae such as *Musca autumnalis* (face flies), *Haemotobia irritans* (horn flies) *Stomoxys calcitrans* (stable flies), heel flies, tsetse flies, blow flies and the like; Diptera: Hippoboscidae (louse flies) such as

*Melophagus ovinus* (sheep ked); Acarina, including ticks, e.g., *Ixodes* spp., *Boophilus microplus*, *Amblyomma* spp., *Hyalomma* spp., *Rhipicephalus* spp., e.g. *Rhipicephalus sanguineus*, *Rhipicephalus appendiculatus*, *Haemaphysalis* spp., *Dermacentor* spp., e.g. *Dermacentor variabilis*, and the like; the Phthiraptera families, including Trichodectidae such as *Bovicola bovis* (important cattle-biting louse), *B. ovis* (sheep-biting louse), *B. equi* (horsebiting louse), Haematopinidae such as *Haematopinus suis* (hog louse), and *H. asini* (horse sucking louse), Linognathidae such as *Linognathus stenopsis* (goat sucking louse) and *L. vituli* (long-nosed cattle louse), and the like; and the Siphonaptera families, including *Pulicidae* such as

5      Archaeopsyllinae (cat and dog fleas), Spilopsyllinae (rabbit fleas), and the like.

10     Accordingly, the present invention provides a method for the prevention, amelioration or control of ectoparasitic infection or infestation in a homeothermic animal which comprises providing to a homeothermic animal in need thereof a prophylactically, therapeutically or pharmaceutically effective amount of a compound

15     of formula I as described hereinabove.

The term "providing" as used herein with respect to providing a compound or substance embraced by the invention, designates either directly administering or applying such a compound or substance, or administering or applying a prodrug, derivative or analog which forms an equivalent amount of the compound or

20     substance at the locus of administration or application or within the body of the target ectoparasite.

Protection of homeothermic animals from the infestation of ectoparasites, particularly of the orders Diptera, Acarina, Phthiraptera or Siphonaptera may be achieved by the application or administration of a prophylactically, therapeutically or

25     pharmaceutically effective amount of a compound of formula I. In actual practice, the formula I compound may be applied to the animal as a dip, spray, pour-on, spot-on, ear tag, collar, medallion, backrubber, oiler, dustbag, powder, lotion, parenteral injection, or the like, preferably as a topical application such as a spray, pour-on or spot-on.

30     The effective amount of the formula I N-phenyl-3-cyclopropylpyrazole-4-carbonitrile compound to be used in the method of invention will vary according to the specific compound used, the mode of application used, the identity of the ectoparasite to be controlled, the degree of infestation, the extent of the ectoparasitic insect population, the nature of the target host, the weather conditions or the like.

Effective dosages in the practice of this invention typically will range from 0.1 mg/kg to 100 mg/kg, preferably about 1.0 mg/kg to 50 mg/kg based on body weight. Naturally, quantities greater than the effective amounts of the formula I compound may be administered, but are not required for the protection of the target animal from the ectoparasite.

The present invention also provides a veterinary composition which comprises a pharmaceutically acceptable carrier and an ectoparasitically effective amount of a compound of formula I. The composition of the invention may be formulated as an aqueous dip for animals such as cattle, sheep, goats or the like or 10 the inventive composition may be prepared as a wettable powder, emulsifiable concentrate, aqueous flowable or the like, which are dispersed in a suitable solvent and applied as sprays to the fur or hide of the animals. Such sprays usually contain about 0.1ppm to 5000ppm and preferably about 0.5ppm to 1000ppm of the active formula I compound. Also preferred is a range of about 0.2 ppm to 20.0 ppm.

15 Advantageously, the compounds of formula I may also be prepared as pour-on formulations and poured on the backs of the animals such as cattle, sheep or companion animals to protect them against infestation by arthropod ectoparasites. The pour-on compositions of the invention are generally prepared by dissolving, suspending or emulsifying the formula I compound in a suitable nontoxic 20 pharmaceutically acceptable diluent for pour-on administration. The diluent must be compatible with the ectoparasiticidal compound and should not be a source of irritation or damage to the animal's skin or hair. Such diluents include mono and polyhydric alcohols, vegetable oils, spreading oils, aliphatic and aromatic hydrocarbons, lower alkyl ketones, esters and fatty acids; such diluents are well-known in the art. Those skilled in the art will readily be able to identify suitable 25 diluents for use in this invention.

In one embodiment of this invention, a pour-on formulation comprises about 0.5% to 30% by weight of the compound of formula I, about 0.5 to 30% by weight of a spreading oil, 30% to 60% by weight of an aliphatic or aromatic hydrocarbon, mono 30 or polyhydric alcohol, lower alkyl ketone or mixtures thereof and 0% to 20% by weight of a vegetable or mineral oil. A more preferred embodiment thereof comprises about 10% to 25% by weight of the compound of formula I, about 20 to 30% by weight of a spreading oil, 40% to 50% by weight of an aliphatic or aromatic hydrocarbon, mono or polyhydric alcohol, lower alkyl ketone or mixtures thereof and 35 5% to 15% by weight of a vegetable or mineral oil.

In another embodiment of this invention, a pour-on formulation comprises 45% by weight of xylene, 25% by weight of cyclohexanone, 15% by weight of said antagonist compound, 10% by weight of corn oil or mineral oil and 5% by weight of other pharmaceutically acceptable diluents such as surfactants, spreading agent, 5 antifoam agents or the like.

Among the spreading oils that can be utilized in pour-on formulations of this invention are fatty acids, fatty acid esters, triglycerides and fatty alcohols including: isopropyl myristate, capryl/caproic acid esters of saturated (C<sub>12</sub> -C<sub>18</sub>) fatty alcohols with waxy fatty acid esters, isopropyl palmitate and the like.

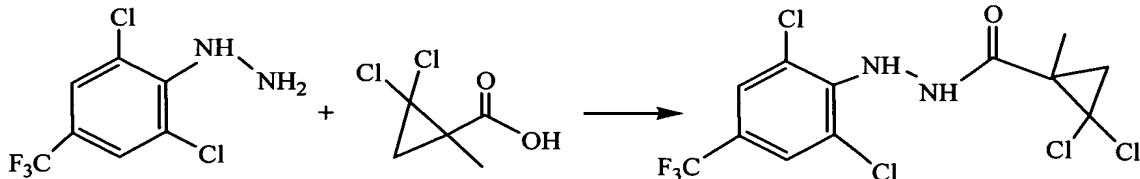
10 Useful alcohols, glycols and ketones in the practice of this invention include: ethyl alcohol, isopropyl alcohol, propylene glycol, dipropylene glycol, benzyl alcohol, dipropylene glycol monoethyl ether, cyclohexanone, methylethyl ketone, methylisobutyl ketone, N-butoxybutylethoxyethanol and the like. Also, the vegetable oils that may be utilized in these formulations include: corn oil, olive oil, peanut oil, 15 sunflower oil, cottonseed oil, soybean oil, and the like. Hydrocarbons that can be used in the formulation of this invention include: xylene, toluene, and the like.

20 Surfactants may also be utilized in the formulations if desired. Those skilled in the art will readily be able to determine which surfactants known in the art will be suitable in the practice of this invention, and will understand how to incorporate such surfactants into formulations of this invention.

In order to present a more clear understanding of the invention, the following specific examples are set forth below. These examples are merely illustrative and are not to be understood as limiting the scope and underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to 25 those illustrated and described herein, will become apparent to persons skilled in the art from the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. The terms HNMR and THF designate proton nuclear magnetic resonance and tetrahydrofuran, respectively. Unless otherwise noted, all parts are parts by weight.

## EXAMPLE 1

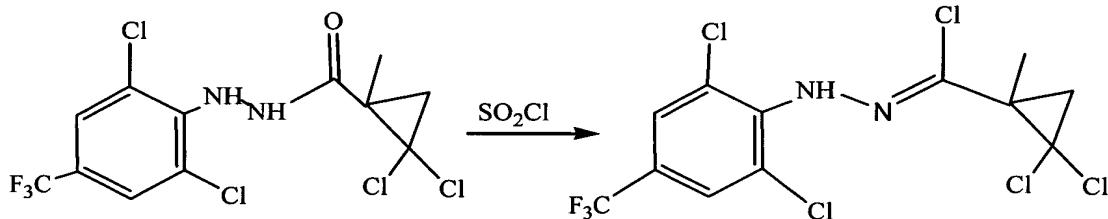
## PREPARATION OF 2,2-DICHLORO-1-METHYLCYCLOPROPYL CARBOXYLIC ACID, N'-[2,6-DICHLORO-4-(TRIFLUOROMETHYL)PHENYL]HYDRAZIDE



5 A mixture of 2,6-dichloro-4-(trifluoromethyl)phenyl hydrazine (25 g, 102 mmol) and 2,2-dichloro-1-methylcyclopropylcarboxylic acid (17 g, 102 mmol) in  $\text{CH}_2\text{Cl}_2$  is treated portion-wise over a 15 min. period with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (20 g, 102 mmol), stirred at room temperature for 18h, diluted with water, stirred for 0.5h and filtered. The filtercake is dried, washed 10 with 1:1 mixture of ether:hexanes and dried *in vacuo* to afford the title product as a white solid, 33 g (82% yield), mp 174-175°C, identified by HNMR and mass spectral analyses.

## EXAMPLE 2

## PREPARATION OF N1-[2,6-DICHLORO-4-(TRIFLUOROMETHYL)PHENYL]-(2,2-DICHLORO-1-METHYLCYCLOPROPANE)-1-CARBOHYDRAZONOYL CHLORIDE

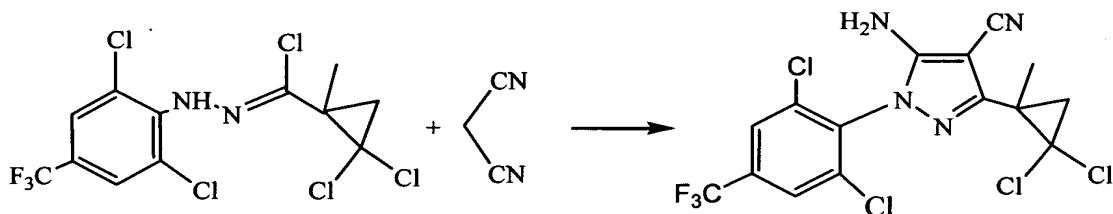


15 A stirred mixture of 2,2-dichloro-1-methylcyclopropyl carboxylic acid, N'-(2,6-dichloro-4-(trifluoromethyl)phenyl)hydrazide (9.4 g, 23.7 mmol) in toluene is treated dropwise with thionyl chloride (7.0 mL, 95 mmol), heated at reflux temperature for 3h, cooled to room temperature and concentrated *in vacuo*. The resultant oil residue is purified through a short bed of silica gel using hexanes as eluent to afford the title

product as a tan solid, 9.1 g (93% yield), identified by HNMR and mass spectral analyses.

### EXAMPLE 3

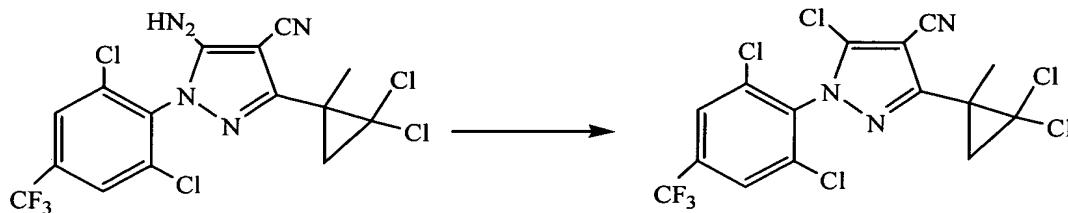
PREPARATION OF 5-AMINO-3-(2,2-DICHLORO-1-METHYLCYCLOPROPYL)-1-  
 5 [2,6-DICHLORO-4-(TRIFLUOROMETHYL)PHENYL]-1H-PYRAZOLE-4-  
 CARBONITRILE



A solution of malononitrile (7.23 mL, 115 mmol) in THF is treated with NaH  
 10 (2.30 g, 57.5 mmol), cooled to 0°C, treated with a solution of [Ex. 2] (9.10 g,  
 23 mmol) in THF over a 0.5h period, stirred at 0°C for 1h, warmed to 20°C, stirred for  
 0.5h and diluted with water and ether. The phases are separated. The organic  
 phase is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The  
 resultant residue is purified by flash chromatography (silica gel, 40% ether in  
 15 hexanes as eluent) to afford the title product as a white solid, 6.15 g (60% yield), mp  
 >200°C, identified by HNMR and mass spectral analyses.

### EXAMPLE 4

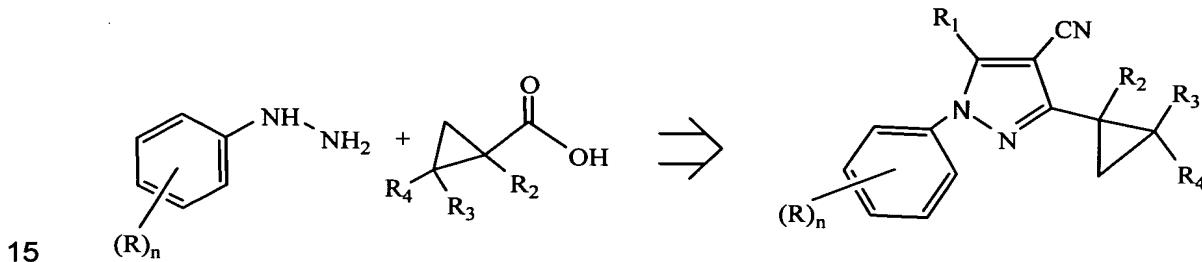
PREPARATION OF 5-CHLORO-3-(2,2-DICHLORO-1-METHYLCYCLOPROPYL)-1-  
 20 [2,6-DICHLORO-4-(TRIFLUOROMETHYL)PHENYL]-1H-PYRAZOLE-4-  
 CARBONITRILE



A mixture of 5-Amino-3-(2,2-dichloro-1-methylcyclopropyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile (5.00 g, 11.3 mmol) in concentrated HCl (30 mL) at 0°C is treated portion-wise with NaNO<sub>2</sub> (7.80 g, 113 mmol) over a 15 min. period, stirred for 1h at 0°C, treated with CuCl<sub>2</sub> (2.24 g, 22.6 mmol), heated slowly to 55°C, stirred at 55°C for 1h, cooled to room temperature and decanted. The remaining solid is dispersed in a mixture of water and ether. The phases are separated. The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The resultant residue is purified by flash chromatography to afford the title product as a red resin, 3.40 g (65% yield), identified by HNMR and mass spectral analyses.

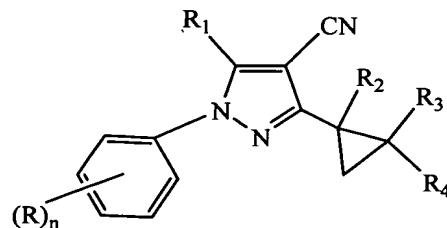
## EXAMPLES 5-40

## PREPARATION OF 3-CYCLOPROPYL-1-PHENYL PYRAZOLE-4-CARBONITRILE DERIVATIVES



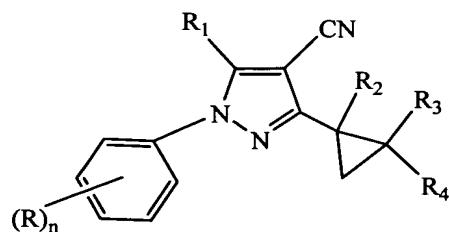
Using essentially the same procedures described in the foregoing Examples 1-4 and employing the appropriate hydrazine and cyclopropylcarboxylic acid, the compounds shown in Table I are obtained and identified by HNMR and mass spectral analyses.

TABLE I



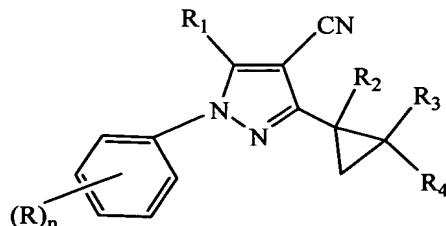
Ex No.	(R)n	R1	R2	R3	R4	Mp °C
5 <sup>a</sup>	2,6-di-Cl-4-CF <sub>3</sub>	H	CH <sub>3</sub>	Cl	Cl	97-98.5
6	2,4,6-tri-Cl	H	CH <sub>3</sub>	Cl	Cl	119-121
7 <sup>a</sup>	2,6-di-Cl-4-CF <sub>3</sub>	H	CH <sub>3</sub>	Cl	Cl	123-125
8	2,6-di-Cl-4-CF <sub>3</sub>	H	CH <sub>3</sub>	H	H	--
9	2,6-di-Cl-4-CF <sub>3</sub>	H	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	H	H	--
10	2,6-di-Cl-4-CF <sub>3</sub>	H	4-Cl-C <sub>6</sub> H <sub>4</sub>	H	H	--
11	2,4,6-tri-Cl	H	CH <sub>3</sub>	H	H	--
12	2,4,6-tri-Cl	H	4-Cl-C <sub>6</sub> H <sub>4</sub>	H	H	--
13	2,4,6-tri-Cl	H	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	H	H	--
14	2,6-di-Cl-4-CF <sub>3</sub>	H	CH <sub>3</sub>	Br	Br	--
15	2,4,6-tri-Cl	H	CH <sub>3</sub>	Br	Br	--
16	2,6-di-Cl-4-CF <sub>3</sub>	H	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	H	H	--
17	2,6-di-Cl-4-CF <sub>3</sub>	H	2,4-di-Cl-C <sub>6</sub> H <sub>3</sub>	H	H	--
18	2,4,6-tri-Cl	H	2,4-di-Cl-C <sub>6</sub> H <sub>3</sub>	H	H	--
19	2,6-di-Cl-4-CF <sub>3</sub>	NH <sub>2</sub>	CH <sub>3</sub>	Cl	Cl	>200
20	2,6-di-Cl-4-CF <sub>3</sub>	Cl	CH <sub>3</sub>	Br	Br	95-98
21	2,6-di-Cl-4-CF <sub>3</sub>	NH <sub>2</sub>	CH <sub>3</sub>	Br	Br	233-235 dec

TABLE I (CONT'D)



Ex No.	(R)n	R1	R2	R3	R4	Mp °C
22	2,6-di-Cl-4-CF <sub>3</sub>	Br	CH <sub>3</sub>	Br	Br	110-114
23	2,6-di-Cl-4-CF <sub>3</sub>	H	H	H	H	102-106
24	2,6-di-Cl-4-CF <sub>3</sub>	NH <sub>2</sub>	H	H	H	158-159
25	2,4,6-tri-Cl	NH <sub>2</sub>	CH <sub>3</sub>	Cl	Cl	185-190
26	2,6-di-Cl-4-CF <sub>3</sub>	Cl	H	H	H	--
27	2,4,6-tri-Cl	Cl	CH <sub>3</sub>	Cl	Cl	128-132
28	2,4,6-tri-Cl	Br	CH <sub>3</sub>	Cl	Cl	133-134
29	2,6-di-Cl-4-CF <sub>3</sub>	Br	CH <sub>3</sub>	Cl	Cl	123-124
30	2,6-di-Cl-4-CF <sub>3</sub>	NO <sub>2</sub>	CH <sub>3</sub>	Cl	Cl	resin
31	2,6-di-Cl-4-CF <sub>3</sub>	I	CH <sub>3</sub>	Cl	Cl	128-130
32	2,6-di-Cl-4-CF <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	Cl	Cl	114-115
33	2,6-di-Cl-4-CF <sub>3</sub>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	CH <sub>3</sub>	Cl	Cl	122-123
34	2,6-di-Cl-4-CF <sub>3</sub>	NHCOT-Bu	CH <sub>3</sub>	Cl	Cl	>220
35	2,6-di-Cl-4-CF <sub>3</sub>	N(CO-cyclopropyl) <sub>2</sub>	CH <sub>3</sub>	Cl	Cl	162-164

TABLE I (CONT'D)



Ex No.	(R)n	R1	R2	R3	R4	Mp °C
36	2,6-di-Cl-4-CF <sub>3</sub>	NHCO-cyclopropyl	CH <sub>3</sub>	Cl	Cl	-
37	2,6-di-Cl-4-CF <sub>3</sub>	N=CHOCH <sub>3</sub>	CH <sub>3</sub>	Cl	Cl	89-91
38	2,6-di-Cl-4-CF <sub>3</sub>	N=CHN(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	Cl	Cl	133-134
39	2,6-di-Cl-4-CF <sub>3</sub>	N=CHO <sub>n</sub> C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	Cl	Cl	oil
40	2,6-di-Cl-4-CF <sub>3</sub>	N=CHOC <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	Cl	Cl	82-84

5 a = Note = Examples 5 and 7 are different compounds. In Example 5, there is -H, -H, at the unlabeled point of the cyclopropyl, while in Example 7 there is -CH<sub>3</sub> at this point.

#### EXAMPLE 41

#### EVALUATION OF THE EFFICACY OF TEST COMPOUNDS AGAINST ADULT CAT 10 FLEAS

The contact activity of a test compound against *Ctenocephalides felis*, adult cat fleas, is evaluated in a coated, glass vial assay. In this evaluation, a solution of test compound in acetone is allowed to dry on the interior surface of a 20 mL vial. Ten unfed adult cat fleas are added to the treated vial and mortality is assessed 15 periodically for up to 48h. All treatments are replicated 2 times. The data are averaged. The results are shown in Table II.

TABLE II

Test Compound (Ex. No.)	Conc. (ug/cm <sup>2</sup> )	% Mortality	
		4h	24h
4	2	100	100
4	0.2	60	100
4	0.002	20	100
5	2	0	33
7	2	0	100
14	2	10	100
15	2	10	80
19	2	0	10
20	2	20	100
21	2	0	0
22	2	0	100
26	2	100	100
27	2	10	100
28	2	0	10
29	2	50	100
29	0.2	20	100
29	0.02	10	100
30	2	0	100
31	2	20	100
32	2	0	100
33	2	20	100
37	2	10	100
39	2	0	70
40	2	0	100
Standard <sup>1</sup>	2	30	100
Standard <sup>1</sup>	0.2	10	100
Standard <sup>1</sup>	0.02	0	100
Control <sup>2</sup>	0	0	0

<sup>1</sup>Fipronil  
<sup>2</sup>Untreated

## EXAMPLE 42

## EVALUATION OF THE EFFICACY OF TEST COMPOUNDS AGAINST ADULT TICKS

The contact activity of a test compound against *Rhipicephalus sanguineus*, 5 adult ticks, is evaluated in a coated glass vial assay. In this evaluation, a solution of test compound in acetone is allowed to dry on the interior surface of a 20 mL vial. Five unfed adult ticks are added to the treated vial and mortality is assessed periodically for up to 48h. All treatments are replicated 2 times. The data are averaged. The results are shown in Table III.

10

Table III

Test Compound (Ex. No.)	Conc. (ug/cm <sup>2</sup> )	% Mortality	
		4h	24h
4	7.80	60	100
4	0.78	60	100
7	7.80	10	80
7	0.78	0	10
14	7.80	50	80
14	0.78	40	40
19	7.80	40	70
19	0.78	0	20
20	7.80	20	50
20	0.78	0	20
21	7.80	0	40
21	0.78	10	10
22	7.80	0	60
22	0.78	20	30
29	7.80	20	60
29	0.78	0	40

TABLE III (CONT'D)

Test Compound (Ex. No.)	Conc. (ug/cm <sup>2</sup> )	% Mortality	
		4h	24h
31	7.80	50	50
31	0.78	10	20
32	7.80	0	30
32	0.78	0	60
Standard <sup>1</sup>	7.80	100	100
Standard <sup>1</sup>	0.78	90	100
Control <sup>2</sup>	0	0	3

<sup>1</sup>Fipronil<sup>2</sup>Untreated

5

## EXAMPLE 43

EVALUATION OF EFFICACY OF TEST COMPOUNDS AGAINST BLOWFLY  
LARVAE

The efficacy of a test compound against newly emerged larvae of *Lucilia sericata*, blowfly, is evaluated using a treated paper/serum bioassay. In this 10 evaluation, a solution of test compound in acetone is applied to a filter paper disc and the disc is allowed to dry. Bovine serum and about 20 newly emerged blowfly larvae are added to the treated paper disc and the mortality is assessed at 24h and 48h. The data are averaged. The results are shown in Table IV.

TABLE IV

Test Compound (Ex. No.)	Conc. (ppm)	% Mortality	
		24h	48h
4	20.0	100	100
4	2.0	100	100
4	0.2	100	100
6	20.0	70	70
6	1.0	10	10
7	20.0	77	90
7	2.0	0	0
9	20.0	0	0
10	20.0	0	0
11	20.0	0	0
13	20.0	0	0
14	20.0	95	100
14	2.0	100	100
14	0.2	50	50
15	20.0	90	90
15	2.0	95	95
15	0.2	0	0
17	20.0	0	0
18	20.0	0	0
19	20.0	75	95
19	2.0	100	100
19	0.2	0	0
20	20.0	100	100
20	2.0	100	100
20	0.2	0	0
21	20.0	90	100
21	2.0	95	100

TABLE IV (CONT'D)

Test Compound (Ex. No.)	Conc. (ppm)	% Mortality	
		24h	48h
21	0.2	0	0
22	20.0	100	100
22	2.0	100	100
22	0.2	0	0
24	10.0	0	0
25	20.0	5	5
25	10.0	0	0
26	20.0	97	97
26	10.0	0	50
26	2.0	0	0
27	20.0	100	100
27	2.0	100	100
27	0.2	0	0
28	20.0	100	100
28	2.0	95	100
28	0.2	0	0
29	20.0	100	100
29	2.0	100	100
29	0.2	15	15
30	20.0	20	20
30	10.0	10	50
31	20.0	97	100
31	2.0	95	100
31	0.2	0	0
32	20.0	91	96
32	2.0	0	0
32	0.2	0	0

TABLE IV (CONT'D)

Test Compound (Ex. No.)	Conc. (ppm)	% Mortality	
		24h	48h
33	20.0	100	100
33	2.0	90	90
33	0.2	0	0
34	20.0	0	0
35	20.0	0	0
36	20.0	10	10
36	10.0	0	--
37	20.0	100	100
37	2.0	0	0
38	20.0	0	0
39	20.0	100	100
39	2.0	70	70
39	0.2	0	0
40	20.0	100	100
40	2.0	0	0
Standard <sup>1</sup>	20.0	100	100
Standard <sup>1</sup>	2.0	100	100
Standard <sup>1</sup>	0.2	0	100
Control <sup>2</sup>	0	0	0

<sup>1</sup>Fipronil<sup>2</sup>Untreated

5           Tables II, III and IV show considerable efficacy for the compounds of the invention. Those compounds displaying zero activity at all tested levels will need to be tested at higher doses to ascertain their effective concentrations.